example" is unclear in claim 7, and that allegedly the term "deep bed filter" in claims 13 and 14 is also unclear.

As discussed above, claims 7, 13 and 14 were canceled in the Preliminary Amendment filed July 23, 1999, thereby rendering the rejection of these claims moot. By the present amendment, claim 29, which corresponds to canceled claim 7, has been amended to delete the phrase "for example." Accordingly, amended claim 29 is clear and definite.

As to the meaning of "deep bed filter," this term is technically the same as a "depth filter." As such, the "deep bed filter" of claim 35, which corresponds to canceled claim 14, is synonymous with a "depth filter." Accordingly, claim 35 is clear and definite as written.

In sum, claims 29 and 35 are clear and definite. Applicants therefore respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejections Under 35 U.S.C. 102(b)

The rejection of claims 1 to 12, which correspond to claims 23 to 34, under 35 U.S.C. §102(b) as allegedly anticipated by Gotschlich *et al.* (J. Exp. Med. 129:1349 (1969)) is respectfully traversed. The Examiner indicates that Gotschlich *et al.* describe "isolating polysaccharides from N. meningitidis which comprises using a detergent, Cetavlon, to rapidly precipitate polysaccharides from whole cells culture" followed by "ethanol is added to the solution and the mixture centrifuged" followed by the " precipitate is then washed again with ethanol, then twice with acetone to remove the detergent and alcohol." [see Office Action, pages 3 and 4]

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (*In re Spada*, 15 USPQ 2d 1655 (Fed. Cir. 1990), *In re Bond*, 15 USPQ 2d 1566 (Fed. Cir. 1990).

Neither originally filed claims 1 to 12, nor presently pending claims 23 to 34 are anticipated by Gotschlich *et al.* For example, as correctly acknowledged by the Examiner in the Office Action at page 5, second paragraph, Gotschlich *et al.* do not teach the use of a deep bed filter or depth filter as required in claim 23. Thus, as Gotschlich *et al.* fail to teach each and every element of claim 23, Gotschlich *et al.* cannot anticipate claim 23, nor any claims

depending therefrom. As such, the rejection under 35 U.S.C. §102(b) over Gotschlich *et al.* (J. Exp. Med. 129:1349 (1969)) is improper and Applicants respectfully request that it be withdrawn.

The rejection of claims 1 to 12, which correspond to claims 23 to 34, under 35 U.S.C. §102(b) as allegedly anticipated by Rienstra *et al.* (EP 0407037 A1) is respectfully traversed. The Examiner indicates that Rienstra *et al.* describe "the isolation of polysaccharides from Gram-negative bacteria and the removal of endotoxin from the polysaccharides." The Examiner further indicates that "the instant claims do not exclude the additional use of phenol or other toxic materials." [see Office Action, page 4]

Neither originally filed claims 1 to 12, nor presently pending claims 23 to 34 are anticipated by Rienstra *et al.* For example, in contrast to claim 23, Rienstra *et al.* describe a method in which alcohol is added to precipitate the released bacteria polysaccharide in the fermentation broth before adding detergent; the detergent is added at a subsequent step (see, for example, page 3, lines 10-13 and lines 18-19; page 4, lines 18-21, lines 40-44 and lines 49-51; and pages 23 to 24, claim 1, step (a) and step (e). Thus, as Rienstra *et al.* fail to teach each and every element of claim 23, Rienstra *et al.* cannot anticipate claim 23, nor any claims depending therefrom. As such, the rejection under 35 U.S.C. §102(b) over Rienstra *et al.* (EP 0407037 A1) is improper and Applicants respectfully request that it be withdrawn.

Rejection Under 35 U.S.C. 103(a)

The rejection of claims 1 to 14, which correspond to claims 23 to 36, under 35 U.S.C. §103(a) as allegedly unpatentable over Gotschlich *et al.* (J. Exp. Med. 129:1349 (1969)) or Schneerson *et al.* (J. Exp. Med. 152:361 (1980)) in view of Hou *et al.* (J. Parenteral Science and Technology 44:204 (1990)) and Lewis *et al.* (U.S. Patent No. 5,589,591) is respectfully traversed. As discussed above, the Examiner indicates that Gotschlich *et al.* describe "isolating polysaccharides from N. meningitidis which comprises using a detergent, Cetavlon, to rapidly precipitate polysaccharides from whole cell culture" followed by "ethanol is added to the solution and the mixture centrifuged" followed by the " precipitate is then washed again with

ethanol, then twice with acetone to remove the detergent and alcohol." Schneerson *et al.* allegedly describe "isolation of polysaccharides from H. influenzae...using a detergent, Cetavlon, to rapidly precipitate polysaccharides from whole cell culture" followed by "ethanol is added to the solution and the mixture is centrifuged" followed by the " precipitate is then washed again with ethanol, then twice with acetone to remove the detergent and alcohol." The Examiner acknowledges that neither Gotschlich *et al.* nor Schneerson *et al.* teach the use of "a polymer filter, deep bed filter, or depth filter." [see Office Action, pages 4 and 5] Hou *et al.* allegedly describe "removing endotoxins from bacterial polysaccharides using a depth filter." Lewis *et al.* allegedly indicate that "raw material must be free of bacterial endotoxins if it is to be used as a parenteral product" and "gel permeation chromatography or ultrafiltration can be used to separate endotoxin and product when the endotoxin is bigger or smaller than the product" and that "in instances when positively charged depth filters cannot be used, such as when the negatively charged product has characteristics similar to endotoxin, ultrafiltration can be used instead."

Neither originally filed claims 1 to 14, nor presently pending claims 23 to 36 would have been obvious in view of Gotschlich *et al.* (J. Exp. Med. 129:1349 (1969)), Schneerson *et al.* (J. Exp. Med. 152:361 (1980)), Hou *et al.* (J. Parenteral Science and Technology 44:204 (1990)) and Lewis *et al.* (U.S. Patent No. 5,589,591) alone, or in any combination, at the time the invention was made.

In order for an obviousness rejection under 35 U.S.C. §103(a) to be proper, *inter alia*, there must be 1) a teaching or suggestion of each and every element claimed; 2) a motivation to combine the cited references in order to produce the claimed invention; and 3) a reasonable expectation of success. [see, for example, M.P.E.P. §2143] However, in the present case, there is no teaching or suggestion to combine the cited references in such a way as to produce the claimed methods, let alone a reasonable expectation of success of producing the claimed methods. In particular, for example, each of the methods described in the cited references is complete in itself: each method is capable of being used to isolate polysaccharides or remove endotoxins without modifying, substituting or adding steps. Thus, as the methods described in the cited references are complete in themselves, there is no motivation for the skilled artisan to

modify the methods, add steps of one method to steps of another method or to substitute steps of one method with steps of another method. In this regard, the Federal Circuit has held that even in situations where the combination of references taught every element of the claimed invention, without a motivation to combine the references, a rejection under 35 U.S.C. §103(a) is improper. *In re Rouffet* 149 F.3d 1350, 1357 (Fed. Cir. 1998). That the cited references describe methods that are complete in themselves indicates that there would have been no motivation to combine or modify them to produce claims 23 to 36.

Furthermore, even if for the sake of argument the cited references indicated that the described methods could be modified, or that method steps could be substituted or added, which they do not, there is no teaching or suggestion which of the many method steps are to be modified, substituted or added, let alone the order in which they are to be performed to produce the specifically claimed methods. For example, the Gotschlich *et al.* method includes the steps of Cetavlon addition, precipitation by centrifugation, homogenizing the precipitate in water with an Omnimixer, recentrifugation, precipitate extraction three or four times with 0.9 M calcium chloride and recentrifugation, followed by addition of ethanol to pooled supernatants of calcium chloride extraction to precipitate and remove nucleic acids. Ethanol is then added to the nucleic acid free supernatant, which precipitates the polysaccharide, which is then centrifuged and washed three times with ethanol, twice with acetone, twice with diethylether and dried *in vacuo*. Further centrifugation steps are employed to completely sediment the precipitate during the ethanol and acetone washes. Proteins were removed from the polysaccharide with phenol/chloroform extraction and, after 6 cycles of homogenization with chloroform-containing butanol, chloroform alone is used for several further cycles. To finally purify the polysaccharide, it is precipitated by addition of ethanol, re-precipitated in ethanol, collected, and washed three times with ethanol, twice with acetone and then vacuum dried (see page 1350-1351). Schneerson *et al.* describe polysaccharide purification employing a number of steps including, for example, DNAse I and RNAse A treatment, followed by pronase treatment, as well as dialysis and ultracentrifugation. Given the number of steps of the Gotschlich *et al.* and Schneerson *et al.* methods it cannot objectively be argued that the skilled artisan would know which of the many steps in the methods to modify, substitute or delete, or the steps that should be

added, let alone the particular steps that would result in producing the specifically claimed methods with a reasonable expectation of success.

Further in this regard, the cited references do not teach or suggest that there is any advantage to modifying or substituting steps or adding a particular step (e.g., depth filter) instead of another (e.g., ultrafiltration, gel permeation chromatography, etc.), let alone any teaching or suggestion as to which of the many method steps are to be combined and the order in which the steps are to be performed, as claimed. For example, Hou *et al.* describe endotoxin removal employing ultrafiltration or a depth type filter (see, page 204, left column, second paragraph). However, Hou *et al.* do not teach or suggest that a depth type filter is any more effective than ultrafiltration for removing endotoxin, or for that matter that a depth type filter is any more effective than any other method for removing endotoxin. Moreover, as acknowledged by the Examiner, Lewis *et al.* also indicate that ultrafiltration may be used to remove endotoxin. Lewis *et al.* further indicate that ultrafiltration is a preferred technique (see, for example, Abstract). Lewis *et al.* additionally indicate that gel permeation chromatography can be used to remove endotoxin. Thus, using the Patent Office's logic, the fact that Hou *et al.* and Lewis *et al.* both describe ultrafiltration or gel permeation chromatography to remove endotoxins indicates that one skilled in the art could have just as easily have been motivated to select ultrafiltration or gel permeation chromatography to combine with the method described by Gotschlich *et al.* or Schneerson *et al.* In this regard, in addition to the above discussed requirements for a rejection to be proper under 35 U.S.C. §103(a), the cited references must be considered as a whole, including portions that would lead away from the invention. [see, for example, M.P.E.P. §2141.02] The fact that both Hou *et al.* and Lewis *et al.* describe ultrafiltration and gel permeation chromatography teaches the skilled artisan away from producing the specifically claimed methods.

In sum, the references fail to teach or suggest modifying any steps, or substituting or adding any step from one method with any step from another method, let alone which of the steps to modify, substitute or add, and in what order the steps should be performed to produce the specifically claimed methods. Thus, it cannot objectively be stated that the skilled artisan would be motivated to modify or combine the references in such a way as to produce the

specifically claimed methods, let alone that there would be a reasonable expectation of success. In addition, that Hou *et al.* and Lewis *et al.* describe ultrafiltration and gel permeation chromatography teaches away from producing the claimed methods. Absent the requisite motivation to modify, add or combine method steps of the cited references, particularly in the manner of claims 23 to 36, absent the reasonable expectation of success, and further in view that ultrafiltration and gel permeation chromatography teach away from producing the claimed methods, the rejection under 35 U.S.C. §103(a) is improper and must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that the claims clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request allowance of the claims now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 03-3975.

Respectfully submitted,

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23. A method for the isolation of polysaccharides, wherein the following steps are carried out:

(a) mixing of a bacterial polysaccharide fraction with a detergent solution;

(b) addition of alcohol to a final concentration which is below the concentration at which the polysaccharide precipitates;

(c) mixing the solution;

(d) filtering the solution by way of a deep bed filter;

(e) separation of the polysaccharide from detergent and alcohol.

24. The method of claim 23, wherein the alcohol is ethanol.

25. The method of claim 23, wherein the separation of the polysaccharide is carried out by the precipitation of the polysaccharide by adding more alcohol.

26. The method of claim 23, wherein the polysaccharides stem from gram-negative bacteria.

27. The method of claim 26, wherein the gram-negative bacteria are selected from the genus consisting of Haemophilus, Neisseria, Klebsiella and Escherichia.

28. The method of claim 23, wherein the detergent is an anionic surfactant.

29. The method of claim 28, wherein the anionic surfactant is an alkyl sulfate.

30. The method of claim 28, wherein the surfactant concentration in the solution added to the polysaccharide fraction in step (a) is at the most 20% (w/w/).

31. The method of claim 30, wherein the surfactant concentration in the polysaccharide solution is 0.1% to 4% (final concentration, w/w).

32. The method of claim 23, wherein in step (b) the alcohol is added to the solution to a final concentration which is approximately 10% below the concentration at which the polysaccharide precipitates.

33. The method of claim 23, wherein the initial concentration of polysaccharides in the polysaccharide fraction is greater than 10 mg/ml.

34. The method of claim 23, wherein the filtration is carried out by means of a polymer filter.

35. The method of claim 34, wherein the polymer filter and/or the deep bed filter is a polypropylene filter.

36. The method of claim 26, wherein the gram-negative bacteria is selected from the group consisting of Haemophilus influenzae (type b), Klebsiella pneumoniae, Neisseria meningitidis and Escherichia coli.